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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,823	06/30/2003	Kiyoshi Uchida	13797-002002 / PH-393US	3073
20985	7590	12/21/2005	EXAMINER DEJONG, ERIC S	
FISH & RICHARDSON, PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			ART UNIT 1631	
DATE MAILED: 12/21/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/611,823

Applicant(s)

UCHIDA, KIYOSHI

Examiner

Eric S. DeJong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-25 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 8-25 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☒ Certified copies of the priority documents have been received in Application No. 08/859,415.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>06/30/2003</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED OFFICE ACTION

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-17 and 19-25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 11 and 19 each recite the limitation of "said numerical value is expressed as $((L+1)/r)^F \cdot \exp(|\Delta G|/RT)$ " and further define the term "r" as "one plus the number of nucleic acid bases between said first target region and said complementary region". Upon review of the instant specification it is clear that applicant has contemplated the use of the above described numerical expression for use in the instantly claimed methods. However, no clear support has been found for the claimed term "r" being equated to "one plus the number of nucleic acid bases between said first target region and said complementary region" as defined in claims 11 and 19.

Page 12, lines 9 and 10 of the instant specification provides one definition of the term "r" as the "...distance between one of double strands and another strand (number of bases between 2 chains (regions) +1)." The terminology used in this definition is

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inconsistent with the terminology recited in the instant claims, which recite "a first and second single stranded sequences identified in within a target sequence of mRNA".

While this definition does provide for adding 1 to a number of bases between 2 chains, it cannot be determined if the terminology used in the disclosure is coextensive in scope with the instantly claimed definition for "r" in claims 11 and 19.

In contrast to the above described definition from the specification, a second definition for the claimed term "r" [provided on page 21, lines 6-8 of the disclosure] states that "...r is expressed as the distance (in terms of number of bases) between the nearest sites in the substantially complementary chain regions. However this definition also does not provide sufficient support for the instantly claimed definition of "r" as it does not disclose adding 1 to the number of bases defining the distance between nearest sites in complimentary regions.

Therefore, the recited definition of the term "r" in instant claims 11 and 19 represents NEW MATTER. Claims 12-17 and 20-25 are also included under this rejection due to their dependence from either claim 11 or 19.

For the benefit of applicant, it is acknowledged that the disclosure does provide sufficient antecedent basis for the claimed term "r" being defined as --an integer representing the number of nucleic acid bases between a first target region and a complementary region--. As such, an amendment to claims 11 and 19 containing the above definition for the term "r" would be sufficient to overcome the above described NEW MATTER rejection.

Claims 8-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must assign the numerical values from either step (c) of independent claim 8 or step (h) of independent claim 18 to each nucleotide within all selected pairs of complementary sequences. In performing either step, every nucleotide within said sequences would be assigned the same numerical value and therefore be rendered indistinguishable. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention. *See also the rejection under 35 USC § 112, second paragraph discussed below.*

b) The disclosure describes methods of designing antisense oligonucleotide

sequences wherein each nucleotide of each selected sequence pair is assigned different numerical values determined on the basis of distance between a pair of complimentary sequences and the bond energy ΔG for each individual sequence selected from all possible pairs of complimentary sequences within a target mRNA or precursor. The disclosure does not describe a method wherein each nucleotide of each selected sequence pair is assigned the same numerical value.

c) The disclosure provides working examples of designing antisense oligonucleotide sequences wherein each nucleotide of a selected sequence pair is assigned different numerical values on the basis of distance between a pair of complimentary sequences and the bond energy ΔG for each individual sequence selected from all possible pairs of complimentary sequences within a target mRNA or precursor. The disclosure does not provide working examples of designing antisense oligonucleotides wherein each nucleotide of every selected sequence pair is assigned the same numerical value.

d) The nature of the invention, designing antisense oligonucleotide sequences on the basis of distance between a pair of complimentary sequences and the bond energy ΔG for each individual sequence selected from all possible pairs of complimentary sequences within a target mRNA, is complex.

e) The prior art does not provide working examples of designing antisense oligonucleotides wherein each nucleotide of every selected sequence pair within a given mRNA target is assigned the same numerical value.

f) The skill of those in the art of designing antisense oligonucleotide sequences is

high.

g) The predictability of designing antisense oligonucleotide sequences on the basis of a distance between a pair of complimentary sequences and the related bond energy, ΔG , is known in the prior art.

h) The claims are narrowly defined in that each nucleotide of the selected pairs of complementary sequences are assigned the same numerical values.

In practicing the claimed invention, the skilled practitioner would be required to assign the same numerical values to every nucleotide within all selected pairs of complementary sequences. In so doing, all selected pairs of complementary sequences would be indistinguishable on the basis of a summation of the numerical values assigned to the nucleotides contained therein. In this event, the skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence how such indistinguishable sequences could be further differentiated so as to select one or more regions that have a low summed value relative to another. Therefore, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss how to further differentiate such antisense oligonucleotide sequences. Finally, said practitioner would turn to trial and error experimentation to determine a relationship between said sequences. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation of "selecting all pairs of sequences on the target mRNA or its precursor... without independently selecting pairs that are shorter than the selected sequences". This limitation appears to contradict itself, as it is unclear how a pair of selected complementary sequence from within a target mRNA or its precursor could ever be "shorter than the selected sequences". Applicants are requested to clarify the metes and bounds of this limitation. Claims 9 –17 are also included under this rejection due to their dependence from claim 8.

For the purpose of continuing examiner, the Examiner has construed that the above described step (a) of instant claim 8 reads on selecting all pairs of complementary sequences from with the target mRNA or its precursor that are separated by at least three nucleotides.

Step (c) of claim 8 recites the limitation of "assigning **the** numerical value obtained in step (b) to each nucleotide of the paired sequences" in lines 13 and 14 of the instant claim (emphasis added). There is insufficient antecedent basis for this limitation in the claim as step (b) is drawn to a plurality of numerical values, wherein

each value is assigned to each of the pairs of sequences selected in step (a). Claims 9-17 are also included under this due to their dependence from claim 8.

Similarly, step (h) of claim 18 recites the limitation of "assigning the numerical value obtained in step (g) to each nucleotide of the sequence". There is insufficient antecedent basis for this limitation in the claim as step (g) is drawn to a plurality of numerical values, wherein each value is assigned to each of the pairs of sequences selected in steps (a) and (b). Claims 19-25 are also included under this rejection due to their dependence from claim 18.

For the purpose of continuing examination, the Examiner has construed the above described limitations to read as --assigning **the numerical values**-- to each nucleotide of the paired sequences (emphasis added).

Claims 8-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships involve the limitations of "selecting one or more regions" and "relative to another region" as recited in steps (e) and (f) of claim 8 and in steps (l) and (m) of claim 18. It is unclear from the instant claims whether the recitation of terms "region" and "regions" relate to specific portions of some or all of the complementary sequences derived from the target sequence utilized in the previously recited method steps or if the claimed terms are intended to encompass other "regions" of a sequence consisting of at least 6 contiguous

nucleotides. If applicants intend the terms “region” and “regions” to specifically refer to portions of the mRNA target sequence selected in the preceding method steps, then the claimed limitations “region” and “regions” further lack proper antecedent basis in the instant claim. Claims 9-17, and 19-25 are also included under this due to their dependence from either of claims 8 or 18.

For the purpose of continuing examination, the Examiner has construed the claimed limitations of a “region” and “regions” to read as one or more sequences found within the target mRNA sequence or its precursor as recited in steps (a) of claim 8 and steps (a) and (b) of claim 18.

Claim 10 recites methods steps indexed by the letters (a)-(h). Confusingly, claim 8, from which claim 10 depends, also recites method steps indexed by the same letters (a)-(f). As such, it is unclear which steps (either from claim 8 or claim 10) are properly being referred to in lines 1, 10, 11, 14, 15, and 17 of claim 10. For the benefit of applicants, the Examiner recommends amending claim 10 to recite method steps consecutively indexed using the letters (g)-(n) in order to avoid confusion.

Conclusion

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

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John S. Brusca 12 December 2005
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PRIMARY EXAMINER